Amendments to the Claims

1. (Withdrawn) A nucleic acid molecule comprising a $P66^{shc}$ coding sequence incorporating at least one mutation as compared to the wild type sequence or the sequence as shown in SEQ ID NO: 1 such that the protein encoded by the coding sequence has at least one serine residue absent or replaced by a different amino acid residue.

2. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is selected from the group consisting of S17, S19, S20, S26, S28, S36, S38, S40, S41, S54, S60, S66, S80 and S102.

3. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is selected from the group consisting of S28, S36 and S54.

4. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is S36 and is replaced by alanine ($p66^{shc}$S36A).

5. (Withdrawn) A polypeptide encoded by a nucleic acid molecule according to claim 1.

6. (Withdrawn) A replicable vector comprising nucleic acid according to claim 1 operably linked to control sequences to direct its expression.

7. (Withdrawn) A host cell transformed with a vector according to claim 6.

8. (Withdrawn) A method of producing a modified $p66^{shc}$ polypeptide comprising culturing a host cell according to claim 7 so that the $p66^{shc}$ polypeptide is produced.

9. (Currently Amended) A method of modulating resistance in cells to oxidative stress by reducing or preventing ~~affecting~~ $p66^{shc}$ ~~signal transduction pathway~~ expression in a cell, said method comprising contacting said cell with an antisense nucleic acid molecule which hybridizes to a nucleic acid encoding SEQ ID NO: 2, ~~agent capable of modulating $p66^{shc}$ gene expression,~~ wherein said contact reduces p66shc expression thereby modulating ~~modulates~~ oxidative stresss resistance in said cells ~~to oxidative stress~~ relative to untreated cells~~, and wherein said agent is an antisense nucleic acid molecule capable of hybridizing to a nucleic acid encoding SEQ ID NO: 2, thereby modulating resistance in said cells to oxidative stress~~.

10. (Cancelled)

11. (Withdrawn) A method according to claim 9 wherein said agent is a vector comprising nucleic acid encoding $p66^{shc}$, said vector being capable of incorporating said nucleic acid into the genome of the cell so that the nucleic acid encoding p66shc is expressed in the cell.

12. (Previously presented) A method of increasing resistance in cells to oxidative stress comprising the step of disrupting the $p66^{shc}$ signaling pathway via introduction of an antisense nucleic acid molecule which hybridizes to a nucleic acid encoding SEQ ID NO: 2, thereby disrupting the $p66^{shc}$ signaling pathway, said disruption increasing resistance to oxidative stress in said cells.

13. (Withdrawn) A method according to claim 12 wherein said step of disrupting the $p66^{shc}$ affects the susceptibility of $p66^{shc}$ to phosphorylation.

14. (Withdrawn) A method according to claim 12 wherein said step of disrupting the $p66^{shc}$ pathway causes a mutant $p66^{shc}$ polypeptide to be expressed such that at least one serine residue present in the wild type $p66^{shc}$ is absent or replaced by a different amino acid residue.

15. (Withdrawn) A method according to claim 14 wherein said serine residue is S36 and is replaced by alanine.

16. (Withdrawn) A method according to claim 14 wherein said mutant polypeptide cannot be serine phosphorylated.

17. (Withdrawn) A method according to claim 12 wherein said disruption affects the ability of a serine/threonine kinase, p38 or MAPK to phosphorylate $p66^{shc}$.

18. (Withdrawn) A method according to claim 12 wherein the step of disrupting the p66shc signaling pathway includes contacting the cell with an antibody binding domain capable of specifically binding to the $p66^{shc}$ polypeptide such that its function is disrupted or prevented.

19. (Previously presented) A method according to claim 12 wherein said step of disrupting the $p66^{shc}$ signaling pathway includes disrupting the $p66^{shc}$ gene expression.

20. (Cancelled)

21. (Cancelled)

22. (Cancelled)

23. (Cancelled)

24. (Currently amended) A method according to claim 9 ~~22~~ wherein said antisense oligonucleotide is RNA.

25. (Cancelled)

26. (Withdrawn) A method according to claim 22, wherein said agent is an antibody binding domain capable of specifically binding to a $p66^{shc}$ polypeptide or fragment thereof.

27. (Currently amended) A method according to claim 9 ~~22~~ wherein said agent is administered for the treatment of a disease selected from the group consisting of arteriosclerosis, ischemic heart disease, lung emphysema, myocardial infarction, stroke, premature aging, cell senescence, Parkinson's, Alzheimer's, cancers, and vascular complications of diabetes.

28. (Withdrawn) A method of increasing resistance to tumor formation in a tissue comprising the step of increasing the expression of $p66^{shc}$ in said tissue.

29. (Withdrawn) A method according to claim 28 wherein the step of increasing the expression of $p66^{shc}$ includes contacting the tissue with an agent capable of increasing expression of $p66^{shc}$ gene.

30. (Withdrawn) A method according to claim 29 wherein said agent is a transcription factor.

31. (Withdrawn) A method according to claim 29 wherein said agent is a vector comprising nucleic acid encoding $p66^{shc}$ polypeptide said vector being capable incorporating said nucleic acid into the genome the cells of the tissue.

32. (Withdrawn) A method of screening for compounds capable of modulating resistance in cells to oxidative stress by modulating the $p66^{shc}$ signaling pathway comprising contacting a candidate compound with a $p66^{shc}$ expression system; determining the amount of a compound of the signaling pathway; and comparing said amount of the component with the amount of the component in the absence of said candidate compound.

33. (Withdrawn) A method according to claim 32 further comprising the step of preparing a pharmaceutical composition

comprising the candidate compound capable of modulating a $p66^{shc}$ pathway and a pharmaceutical acceptable carrier.

34. (Withdrawn) A method according to claim 32 wherein said step of determining the amount of a compound of the signaling pathway is an enzyme activity assay.

35. (Withdrawn) A method according claim 32 wherein said candidate compounds include nucleic acid sequences, antibody binding domains, and protein nucleic acids.

36. (Previously presented) A method of reducing intracellular levels of reactive oxygen species (ROS) in a cell, said method comprising the step of contacting said cell with an agent capable of inhibiting the expression of a $p66^{shc}$ polypeptide in said cell, wherein said agent is an antisense nucleic acid molecule capable of hybridizing to nucleic acid encoding SEQ ID NO: 2, thereby reducing intracellular levels of ROS.

37. (Previously presented) A method according to claim 36 wherein said contact with said nucleic acid reduces or prevents expression the $p66^{shc}$ polypeptide.

38. (Withdrawn) A method according to claim 36 wherein the agent is an antibody binding domain capable of specifically binding to the $p66^{shc}$ polypeptide such that its functions are inhibited or prevented.

Claims 39-41 (Canceled)

42. (Withdrawn) A method of determining the presence or absence of a $p66^{shc}$ nucleic acid or a mutant, variant derivative or allele thereof in a biological sample, comprising the step of contacting said sample with a nucleic acid molecule capable of hybridizing specifically with said $p66^{shc}$ nucleic acid or a mutant, variant derivative or allele thereof and determining whether or not hybridization has taken place.

43. (Withdrawn) A method of determining the presence or absence of a $p66^{shc}$ polypeptide or a mutant, variant derivative or allele thereof in a biological sample, comprising the step of contacting said sample with an antibody binding domain capable of binding $p66^{shc}$ or a mutant, variant derivative thereof and determining whether or not binding has taken place.

44. (Withdrawn) An expression system comprising a nucleic acid vector having a $p66^{shc}$ coding sequence or fragment thereof inserted therein.

45. (Withdrawn) A method according to claim 10 wherein said agent is a vector comprising nucleic acid encoding $p66^{shc}$, which when expressed in a cell results in production of $p66^{shc}$.

Claims 46-52 (Cancelled)

53. (New) The method of claim 9, performed in vitro.

54. (New) The method of claim 9, performed in vivo.

55. (New) The method of claim 9 wherein said antisense is cloned into a vector.

56. (New) The method of claim 9, wherein said cells are contacted with a vector expressing said antisense molecule.

57. (New) The method of claim 24, wherein aid cells are contacted with a vector expressing said antisense molecule.

58. (New) A method of reducing expression of $p66^{shc}$ in a cell, said method comprising contacting said cell with an effective amount of an antisense nucleic acid molecule which hybridizes to a nucleic acid encoding SEQ ID NO: 2, wherein said contact reduces $p66^{shc}$ expression in said cell.

59. (New) The method of claim 58, wherein said nucleic acid is RNA.

60. (New) The method of claim 58, wherein said cell is contacted with said antisense nucleic acid cloned into an AAV2 vector.

61. (New) The method of claim 58, performed in vitro.

62. (New) The method of claim 58, performed in vivo.